Author’s response to reviews

Title: Long-term follow-up of nonspecific small bowel ulcers with a benign course and no requirement for surgery: is this a distinct group?

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Author’s response to reviews: see over
Dear the Editors,

Please find the revised manuscript. All changes made were highlighted with red.

My point-to-point response to the comments was presented in the cover letter. One reviewer called Masahiko Inamori considers this is an article of importance in its field. I hope my response will eliminate the other reviewers’ concerns.

One reviewer said there are many mistakes in the regulations and English grammars. I have tried my best to minimize language mistakes. I used the service of language editing provided by International Science Editing before the initial submission. You may find my email communication with International Science Editing concerning their copyediting work on my manuscript in the attached file.

I look forward to your decision soon.

Best regards,

Weifeng Wang, MD
Reviewer: Masahiko Inamori

Major Compulsory Revisions

#1. In the paragraph of pathological evaluation of method, you should provide in detail from which portion of ulcers did you take the biopsy specimens. (the bottom, edge or both?)

We tried to take the biopsy specimens from the edge of ulcers but sometime the forceps was larger than the ulcers and covered all the ulcers.

#2. You used the word “related gastrointestinal symptoms” in the second paragraph of discussion. However, in the section of result, you reported that the gastrointestinal symptoms did not always correlate with the presence of ulcers, and the word “related” should be eliminated.

Thanks. I delete it as suggested.

#3. In the third paragraph of discussion, you mentioned the difference of indications for investigation between previous reports and this study. Considering selection bias, you should illustrate the clinical features of patients who underwent colonoscopy at Chinese PLA General Hospital. (the indications for investigation in all the patient who underwent colonoscopy at Chinese PLA General Hospital)

Thanks. I added this part to ‘Methods’.
Reviewer: Takayuki Matsumoto

**Reviewer's report:**

The authors address the nature and long-term outcome of non-specific small bowel ulcers, which were not, unfortunately, well-defined in the manuscript.

**Major comments:**

1. The authors defined ulcer as "being no smaller than 3mm in diameter with significant depth". However, most ulcers in this manuscript were small (almost near 3mm) and superficial, typically observed in Fig. 1. This may raise the possibility that most cases in this manuscript can be categorized as "Non-specific small bowel ulcers" as the other papers defined as "erosions or nonspecific ileitis".

2. These small ulcers or erosions in ileum could be found in 1-3% of the screening colonoscopy or colonoscopy for diarrhea patients. (Joeng SH, et al. J Gastroenterol Hepatol 2008; 23:51-55. and Ref. 25.

3. Are there any possibilities that the clinical course and outcome differ in the present patients and reported cases as nonspecific small bowel ulcer (p.7) because the present cases include mild ileitis sometimes observed in the screening colonoscopy?

   **My explanation:**

   These three questions are correlated with each other. The concern was raised regarding the differentiation of our case series with non-specific small bowel ulcers from those with erosions or nonspecific ileitis. I would like to address these three questions together.

   First of all, erosion and ulcer are pathological terms. Actually one may feel it is difficult to distinguish small ulcers from erosions macroscopically. The definition of ulcers as being no smaller than 3mm in diameter with significant depth [Ref. 16] which has been reported in the literature facilitates the evaluation of small ulcers and erosions, hence it is practical for the clinical studies.

   Both the terms of nonspecific small bowel ulcers and nonspecific ileitis can be found in the literature. To my knowledge, the entity of nonspecific ileitis hasn’t been clearly defined so far, nor has nonspecific ulcer of small intestine. Hence it is worthy of further exploration. There are reports of erosions and small ulcers revealed during ileoscopy, and some of them were nonspecific [J Gastroenterol Hepatol 23 (2008) 51–55; Am J Gastroenterol 2003;98:1512–1515; Dig Liver Dis. 2003;35:784-787; Dis Colon Rectum 1985;28:499-501.]. Unfortunately data on long-term follow-up was lacking and the nature of these lesions was unknown. We believe our data is a useful complement to this topic.

4. The present cases include non-symptomatic patient (case 7) and single small erosion only on ileocecal valve. Those patients could be non-symptomatic, and therefore, it is not always link to the IBS symptoms. It is not suitable to sum up these cases to a single syndrome.

   There are 6 cases presenting lower GI symptoms suggestive of functional bowel
disorders and one case without GI symptoms. They are all included because they fulfilled the inclusion and exclusion criteria that were stated in the methods. Symptoms weren’t included in the criteria. Several distinct syndromes regarding nonspecific small bowel ulcers have been described, which suggested nonspecific small bowel ulcers is heterogeneous. Maybe it is also heterogeneous in our case series. It is reasonable to divide these patients into two groups according to the symptoms however it need further evidence from more studies on this topic.

5. Matsumoto, et al. defined CNSU (Ref. 18) as having more than 20 ulcers in the small bowel. The authors should describe. Yes, I’ll add this part to my manuscript. It’s my responsibility to truly reflect the reference’s idea.

6. In discussion (p.8), the authors described that the negative effects of %-ASA as a basis to deny inflammatory bowel disease. However 40% of the IBD patients do not respond to 5-ASA. I agree with the reviewer. This part has been rewritten.

Minor comments:
1. How about the fecal occult blood test?
The fecal occult blood tests in all patients were negative which contributed to that patients were suspected of functional bowel disease for a long time.
2. Table 1; “female” to “Female”
Yes.
Reviewer: Kazuhide Higuchi

Reviewer's report:

Comment
The paper was written in a careless manner. There are many mistakes in the regulations and English grammars. Some sentences are put without a need. This paper does not follow the general rules of writing a paper. Most of the literature reported that the nonspecific small bowel ulcers are associated with anaemia, hypoproteinemia and/or stenosis. However, in this study, they only reported abdominal pain and diarrhea. I wonder if the data are collected carefully or not.

I respect the reviewer's effort putting on this manuscript. I want to clarify his major concerns.

As a non-native English speaker, I used the service of language editing provided by International Science Editing before the initial submission. You may find my email communication with International Science Editing in the cover letter supplied to the Journal.

Just as the reviewer mentioned, most of the literature reported that the nonspecific small bowel ulcers are associated with anaemia, hypoproteinemia and/or stenosis, however there are also reports of erosions and small ulcers revealed during ileoscopy, and some of them were nonspecific [J Gastroenterol Hepatol 23 (2008) 51–55 ; Am J Gastroenterol 2003;98:1512–1515; Dig Liver Dis. 2003;35:784-787; Dis Colon Rectum 1985;28:499-501.]. Unfortunately data on long-term follow-up was lacking and the nature of these lesions was unknown. We believe our data is a useful complement to this topic.

In order to ensure the accuracy of the data, the electronic data of these seven patients have been checked with patients one by one.

Title (page 1) Grammar mistake
Long-term follow-up of nonspecific small bowel ulcers with a benign course and no requirement for surgery: are these a distinct group?
Correct: is this
Thanks, I agree with the reviewer.

Abstract (page 2)
1- All seven patients (aged 54.7 years) presented
Q: Is this median age or mean age??
It is mean age and I have labeled it in the manuscript.
2-Keywrods: where are the keywords?
The keywords have been added to the manuscript.

Methods (page 3)
Inclusion criteria, exclusion criteria, are not written well.
What are the data you collected from the patients?
The clinical records were collected including history of present illness, laboratory findings, radiological and endoscopic examination, the pathological findings of
biopsy specimens in the initial workup and follow-up. The inclusion and exclusion was based on these records.

Results (page 5)

# You said in methods (page3) : We reviewed the medical records of all patients who had undergone either balloon enteroscopy or ileoscopy in 2000–2005 at the Chinese PLA General Hospital, a tertiary referral center located in Beijing, China. So, how many patients did enteroscopy in this study?

# You said in results (page 5 line 3): The major indications for colonoscopy were diarrhea and/or abdominal pain/discomfort. So, how about the indication of enteroscopy?

You said in results (page 5 line 25): All the ulcers were identified by ileoscopy on the first visit, when terminal ileum intubations (10–25 cm) were performed routinely during colonoscopy. So, how about enteroscopy results? It is a controversy!

I wonder enteroscopy was done or not in the present study!

Enteroscopy is indicated in the following clinical situations: bleeding from the gastrointestinal tract of obscure cause; exploration of abnormalities seen on small bowel radiography; unexplained diarrhea. All the data of enteroscopy were also reviewed and no one fulfilled the inclusion criteria except one case who were found to be suffering from ileal ulcers by ileoscopy during first visit and undertook enteroscopy during the follow-up(indicated in Tab 3). That case was the only one out of these 7 cases who undertook enteroscopy. That is why I said ‘All the ulcers were identified by ileoscopy on the first visit’.

(Page 5 line 11): Various empirical treatments were applied, including probiotics and 5-asalazine (5-ASA), except in two patients for whom no medication was prescribed.

Q: What are the doses and what are the duration of treatment???

Several kinds of probiotics were given at the recommended doses. The patients took 4g 5-asalazine per day for at least 3 months.

(Page 5 line 18): No patient had a history of chronic NSAID use before the initial diagnosis.

Q: This sentence is an exclusion criterion, so why you mention it as a result. !!!

Thanks, I delete this sentence.

(Page 6 line 15): A final endoscopy showed persistent ulcers in more than half the patients, whereas one patient (case 6) had recurrent ulcers and two patients (case 2 and case 5) had self-limiting ulcers.

Q: you should mention the number and/or the percentage (%) because it is a result not a discussion.

Thanks. The percentages are given as suggested.

Discussion

-Not written well

(Page 8 line 1): Our case series is similar to the case reported by Borsch et al., which was assumed to be IBS before a diagnosis of nonspecific small bowel ulcers was made [5].


The reference number [5] should be put after the name of the author.
Thanks. I revise it as suggested.
(Page 8 last paragraph): Two patients became chronic aspirin users during follow-up. their final results showed that, in this study, chronic aspirin use did not interfere with the clinical course and no NSAID-related enteropathy ensued since aspirin may be safer than other NSAIDs during enteropathy [35].
Q: why you put this reference here? I think you speak about your result!!
Thanks. I rewrite it.
(Page 9 line 2): In our study, a variety of empirical medicines was used, including 5-ASA [18], probiotics, and herbal medicines. Probiotics seemed partly effective in two patients with diarrhea, but they had no direct effect on the ulcer itself.
Q: why you put this reference here? I think you speak about your result!!
Thanks. I amend it.
Tables
Table 1 (page 13): the first row is not regulated
Table 2 (page 14): -The first row is not regulated
-First time to see these abbreviations: TI & V
Thanks. I revise it as suggested.
Other grammar mistakes......
Thanks. All the grammar mistakes listed here are corrected.